1400/2110

PATENT

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| In re Application of | Green et al. | ) Art Unit: | N/A |
| Serial Number | 09/823,992 | ) Examiner: | N/A |
| Filed | APRIL 3, 2001 | ) Atty Ref: | GRE001 |

For: MASS SPECTROMETRY AND METHODS OF MASS SPECTROMETRY

**THE COMMISSIONER OF PATENTS AND TRADEMARKS**
**Washington, D.C. 20231**

*Sir:*

The below identified communication(s) or document(s) is(are) submitted in the above application or proceeding:

- ☐ Amendment/Response
- ☒ Priority Document
  **GB-0029040.3**
- ☐
- ☐
- ☐ Issue Fee Transmittal
- ☐ Check in the Amount of $
- ☐ Assignment
- ☐ Associate Power of Attorney

☐ Please charge **Deposit Account Number 04-1075** for any deficiency or surplus in connection with this communication. A duplicate copy of this sheet is provided for use by the Deposit Account Branch.

*Respectfully submitted,*

Everett G. Diederiks, Jr.
Attorney for Applicant
Registration Number: 33,323

Date: May 10, 2001

The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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Signed

Dated 17 APR 2001

0029040.3

**Patents Form 1/77**

Patents Act 1977
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29 NOV 2000

The Patent Office

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1/77

# Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 85.74495

2. Patent application number *(The Patent Office will fill in this part)* — 0029040.3

29NOV00 E587475-1 D00027
P01/7700 0.00-0029040.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Micromass Limited
Floats Road, Wythenshawe
Manchester, M23 9LZ
United Kingdom

Patents ADP number *(if you know it)* 06961020001

If the applicant is a corporate body, give country/state of incorporation — United Kingdom

4. Title of the invention — Orthogonal Time of Flight Mass Spectrometer

5. Name of your agent *(if you have one)* — Frank B. Dehn & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

179 Queen Victoria Street
London
EC4V 4EL

Patents ADP number *(if you know it)* — 166001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*
*See note (d))*

Yes

# Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

| | |
|---|---|
| Continuation sheets of this form | - |
| Description | 2/ EE |
| Claim(s) | - |
| Abstract | - |
| Drawing(s) | - |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | - |
| Translations of priority documents | - |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | - |
| Request for preliminary examination and search *(Patents Form 9/77)* | - |
| Request for substantive examination *(Patents Form 10/77)* | - |
| Any other documents *(please specify)* | - |

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 29 November 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

P.M. Jeffrey
01273 244200

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a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*
b) *Write your answers in capital letters using black ink or you may type them.*
c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s) of the form. Any continuation sheet should be attached to this form.*
d) *If you have answered 'Yes', Patents Form 7/77 will need to be filed.*
e) *Once you have filled in the form you must remember to sign and date it.*
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**Increasing Dynamic Range of an Orthogonal Time of Flight Mass Spectrometer Using Fast Sensitivity Switching During Acquisition.**

**Background.**

The use of a time to digital converter (TDC) (ion arrival counter ) as an acquisition device for oaTOF results in a restriction to the ultimate dynamic range for the detection of short-lived signals. Even after the application of dead time correction software, ion signals resulting in more than 1 ion arrival, on average,per pushout event at a given m/z value, result in saturation , non linear response and inaccurate exact mass determination.
This limitation is accentuated in GC MS applications because of the narrow chromatographic peaks presented to the TDC which can commonly be in the order of 2 seconds wide at the base. In this case, with the system operating at 25KHz pushout frequency, a total of 25,000 ions can be recorded for a given m/z value during a chromatographic peak elution before significant non linearity of response.

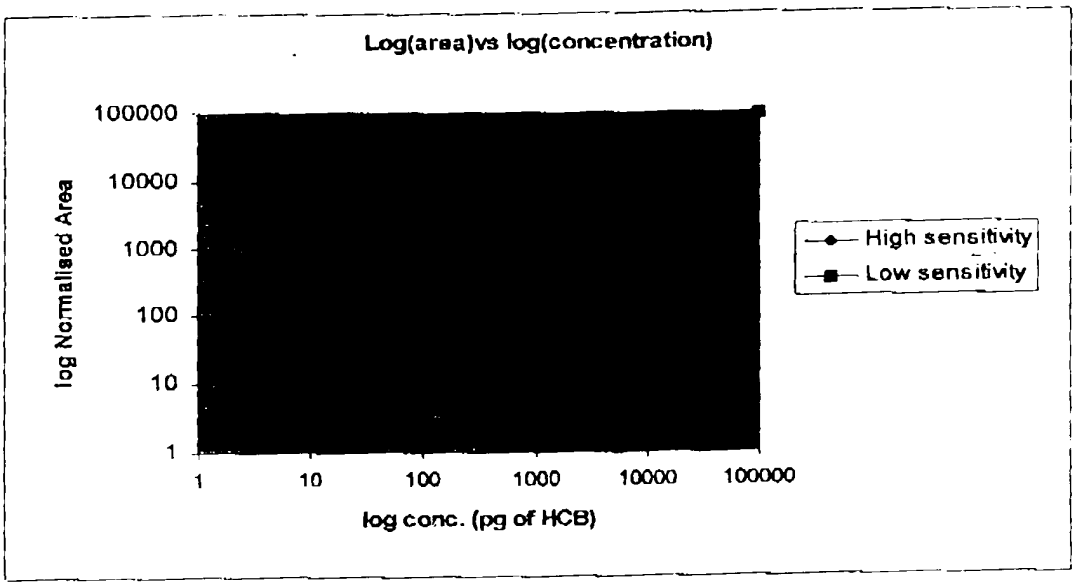
**Principle of operation**

To extend the dynamic range, the system has been designed to alternate between two sensitivity ranges during an acquisition. One range is tuned to be at high sensitivity. The second is adjusted to be at a lower sensitivity than the first by a factor of up to 100x. The two data streams are stored as two discrete functions presenting two discrete data sets. Once the ratio of the high sensitivity to low sensitivity data has been determined the data can be massaged to yield linear quantitative calibration curves over 4 orders of magnitude. Furthermore, the system can be arranged so that exact mass data can be extracted from either trace. Therefore, if a particular eluent produces a mass spectral peak which is saturated in the high sensitivity data set and therefore exhibits poor mass measurement accuracy, the same mass spectral peak may be unsaturated and correctly mass measured in the lower sensitivity trace. By using a combination of both traces, as sample elutes exact mass measurements may be produced over a wide range of sample concentration.

**Description of design**

A set of Z focussing lenses are installed into the outer ion source in a field free region of the optics. These are connected to a fast switching power supply capable of suppiying from -100 to +100V DC. Initially the system is tuned to full sensitivity. The Z focusing lens voltage is than varied manually until the desired lower sensitivity is reached. Acquisition then results in fast switching of the Z lens power supply between two (or more) pre-determined voltages between each spectrum. Spectra are stored as seperate functions to be post processed.

**Preliminary results**




The graph above demonstrates four orders of magnitude dynamic range using a combination of data from both the high and low sensitivity data sets. The system was tuned to give a ratio of approx. 80:1 between the high and low sensitivity data sets. The experiment allowed equal acquisition time for both data sets alternating between the two sensitivity ranges between spectra.
Standard solutions ranging in concentration from 10 pg – 100ng of HCB were injected via the GC. The peak area response for the reconstructed ion chromatogram of m/z 283.8102 was plotted against the concentration. The results from the low sensitivity data set were multiplied by 80x before plotting, to normalise them to the high sensitivity data set.

**Specific features**
Exact mass measurement can be made using a single point lock mass common to both high and low sensitivity ranges.

Utilising Z focusing minimises any change in resolution, mass position and spectral skew associated with focussing/ deflection in the Y direction.

The relative dwell time for the high and low sensitivity functions can be varied. This will allow minimum sensitivity loss for the high sensitivity trace whilst still allowing the maximum increase in dynamic range

This is the first time that this approach has been used with oaTOF technology.

At least 1 order of magnitude increase in dynamic range can be achieved, from 3.25 – 4.25 orders of magnitude.